REMARKS

Claims 71, 82-92, and 97-110 are pending after entry of this paper. Claims 71, 81-104, 106, 108, and 110 have been rejected. Claims 105, 107 and 109 have been withdrawn from consideration. Claims 1-70 and 72-81 have been previously cancelled without prejudice. Claims 93-96 have been currently cancelled without prejudice. Applicants reserve the right to pursue withdrawn and cancelled claims in a divisional or continuing application.

Claims 71, 82, 84-92, and 97-102 have been amended to overcome the claim objections of record and the rejections raised under 35 U.S.C. § 112, first and second paragraphs.

No new matter has been introduced by the claim amendments presented herein. Reconsideration and withdrawal of the pending rejections in view of the above claim amendments and below remarks are respectfully requested.

Response to Claim Objections

Claims 71, 85, 86, 88-90, 93, 95, 97 and 99-101 are objected to due to the following informalities: grammatical errors. In particular, according to the Patent Office, claims 71, 86, 90, 93, 95, 97, 99 and 101 recite a grammatical error in the phrase "having biological activity like as activity of a compound of a purine system of a body." (Office Action, p. 5).The Patent Office helpfully suggests amending claims to state "having biological activity of a compound of a purine system." Id. However, without disclaimer of, or prejudice to, the subject matter recited therein, applicants have amended claims by deleting said recitation from the claims.

Furthermore, according to the Patent Office, claims 71, 86, 90, 93 and 95 recite the grammatical error in the phrase "nucleus and non-nucleus cells." (Office Action, p. 6). The

Patent Office helpfully suggests amending claims to replace the term "nucleus" with the term "nucleated." Id. Applicants respectfully complied and amended the claims accordingly.

Claim 82 recites at line 3 "pancreatic," which according to the Patent Office appears to be a typographic omission of "pancreatic diabetes" recited in canceled claim 73. Id. However, it appears that the recitation in question was a typographical error. Instead of "pancreatic," applicants respectfully assert that the recitation should have been "pancreatitis," which is an inflammation of the pancreas.

Claim 85 recites at line 2 "insulin resistance,." where a period appears after the comma. Id. Moreover, claim 85 recites at line 2 "hyper fatty academia," while according to the Patent Office, it should be "hyper fatty acidemia." Applicants respectfully complied and amended claim 85 to recite "hyper fatty acidemia" and removed the period after comma.

According to the Patent Office, claim 88 incorrectly recites "ischemic diseases of heart," while claim 89 incorrectly recites "ischemic diseases of human brain." Both claims have been amended. Claim 88 has been amended to recite "ischemic heart disease" and claim 89 has been amended to recite "brain ischemia."

Finally, according to the Patent Office, claim 100 incorrectly recites "cholestasis icluding pregnants," while claim 102 incorrectly recites "embolism after surgery with vessel." Both claims have been amended. Claim 100 has been amended to recite "cholestasis of pregnancy" and claim 102 has been amended to recite "venous embolism caused by surgery."

In light of these claim amendments, applicants respectfully believe that the instant claim objections are moot and respectfully request that these objections be withdrawn.

Response to Rejections under 35 U.S.C. § 112, first paragraph

Claims 71, 81-104, 106, 108 and 110 have been rejected under 35 U.S.C. § 112, first paragraph because "the specification, while being enabling for thymus involution and diseases known in the prior art such as acute hypoxia or myocardial infarct, [etc.] . . . does not reasonably provide enablement for the full scope of the diseases treated in the claimed method such as the specific diseases recited in claims 82, 84, 85, 87, 89, 91, 92, 94, 96, 98, 100 and 102 not known in the prior art." (Office Action; p. 7). Applicants respectfully disagree with the above assessment provided by the Patent Office.

However, in order to expedite prosecution and without disclaimer of, or prejudice to, the subject matter recited therein, applicants have amended claims 71, 82, 84-92, and 97-102 to clarify that the cyclic bioisostere(s) identified in the instant specification treats a particular dysfunction such as the acidosis (*e.g.*, ¶¶ [0092]-[0143]; Sections 1 and 2 of the specification as published) that can come about as a manifestation of chronic pneumonia, tissue hypoxia, arterial hypoxia, pleurisy, obstructive bronchitis, anemias, peritonitis, pancreatic diabetes, febrile state, and rheumatoid arthritis to name the few, well known causes of acidosis (e.g., ¶ [0009]). For example, applicants readily showed a working example of administrating 37 different compounds to an *in vitro* model (i.e., embryonic fibroblasts of mouse NIH-3T3) of a cellular system. The compounds were capable of penetrating into the endocellular space and showed that they can irreversibly attract up to 4 electrons and protons, thereby promoting the intensification of the processes of tissue respiration and appreciable decrease of a metabolic endocellular acidosis. (see ¶ [0091] of the specification as published). Similarly, applicants conducted other experiments and presents plethora of evidence to demonstrate that this family of compounds, in addition to acidosis, can be used to treat oxygen deficiency (Claim 86), reduce the excess of free

radicals (Claim 90), used to treat and/or as a prophylactic in decreasing the aggregation of thrombocytes and erythrocytes (Claim 97 and Claim 101), and used as hepatoprotectant (Claim 99). A skilled artisan could readily comprehend that the treatment of, for example, pancreatitis with the cyclic bioisosteres identified in the instant specification may not necessarily cure the patient of the pancreatitis, but it will have an effect on the endocellular pH and, specifically, normalization effect of the endocellular pH to the physiologically acceptable levels, which may have many debilitating effects such as, for example, the vessels expand and venous pressure drops down. (see ¶ [0011] of the specification as published).

Applicants respectfully contend that the method as recited in the presently amended claims is fully enabled and those skilled in the art would be able to practice said method without any undue experimentation. Applicants respectfully request that the rejections under 35 U.S.C. §112, first paragraph be withdrawn.

Response to Rejections under 35 U.S.C. § 112, first paragraph

Claims 82, 84, 85, 87, 89, 91, 92, 94, 96, 98, 100, and 102 have been rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement because the claims allegedly recite specific diseases that are not described in the specification. Specifically, the Patent Office points to the specific diseases recited in claims 82, 84, 85, 87, 89, 91, 92, 94, 96, 98, 100, and 102. Applicants respectfully disagree.

However, in order to expedite prosecution and without disclaimer of, or prejudice to, the subject matter recited therein, applicants have amended claims 82, 84, 85, 87, 89, 91, 92, 94, 96, 98, 100, and 102 to clarify that the cyclic bioisostere(s) identified in the instant specification treats a particular dysfunction such as the acidosis (*e.g.*, ¶¶ [0092]-[0143] of the

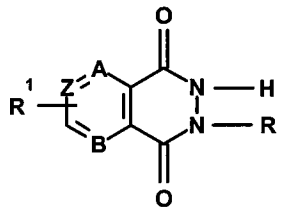
specification as published; see specifically sections 1 and 2) that can come about as a manifestation of, for example, chronic pneumonia. With reference to claim 82, for example, the claim now recites "wherein the reversible abnormal changes in pH of nucleated and non-nucleated cells is caused by . . . .[for example] chronic pneumonia. . . " In other words, the cyclic bioisostere still treats the abnormal pH change and the claim now recites the possible causes of the acidosis. Contrary to the position taken by the Patent Office, a specification reasonably conveys to one skilled in the art that the applicants had possession of the claimed invention because "[t]he specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public." (see MPEP 2164.05(a)). For example, it was well known at the time of filing that respiratory acidosis develops when the lungs do not expel carbon dioxide adequately, a problem that can occur in diseases that severely affect the lungs, such as chronic pneumonia, *i.e.*, inflammation of the lungs that persists for an extended period of time. A skilled artisan would recognize this correlation. Thus, applicants do not dispute that some of the causes for the claimed disorders were not recited in the specification, but the specification need not disclose what was well-known in the art at the time of filing because the list provided in the specification was merely exemplary and not to be taken as an all inclusive list of diseases that may cause the underlying disorders treated herein. Applicants respectfully request that the rejections under 35 U.S.C. §112, first paragraph be withdrawn.

Response to Rejections under 35 U.S.C. § 112, second paragraph

Claims 71, 81-104, 106, 108 and 110 have been rejected under 35 U.S.C. 112, second paragraph as being indefinite. Specifically, according to the Patent Office, it is unclear

whether the method requires the administration of the compound having the general structural formula recited in claim 71 or whether the method encompasses all "cyclic bioisostere" of the compound having said general structural formula. Applicants respectfully disagree with the interpretation put forward by the Patent Office.

However, in order to expedite prosecution and without disclaimer of, or prejudice to, the subject matter recited therein, applicants respectfully assert that since bioisosteres are substituents or groups with similar physical or chemical properties which produce broadly similar biological properties to a chemical compound, those skilled in the art would understand that when the applicants say "cyclic bioisostere of derivatives of a purine system," the applicants refer to the compounds that have the chemical formula of



and the substitutions listed after the formula produce a family of claimed bioisosteres. In other words, the scope of the claims is defined by the general formula and the provided list of substitutions, e.g., "R^1 is selected from the group consisting of."

Applicants respectfully request reconsideration and withdrawal of the 35 U.S.C. §112, second paragraph rejection in light of the provided explanation.

Response to Rejections under 35 U.S.C. § 102(b)

Claims 71, 82, 86, 88, 90, 95-98, 101-104, 106, 108, and 110 have been rejected under 35 U.S.C. 102(b) as being anticipated by Minin, et al. (U.S. Patent 5,512,573, already of

record). Specifically, the Patent Office contends that Minin discloses the administration of luminol as an antioxidant to treat various disorders disclosed in the previously pending claims. (Office Action; p. 14-15). The Patent Office notes

> [t]hat intracellular acidosis (or reversible abnormal changes of pH of cells of the living body) (claim 71), oxygen deficiency in cell (claim 86), increasing the aggregation of thrombocytes and erythrocytes (claim 97) or prophylaxis of decreasing the aggregation of thrombocytes and erythrocytes (instant claim 101) is merely considered to be new function or the unknown property or the mechanism of action of a treatment, 5-aminophthaloylhydrazide and its salts administered in effective amounts. It has been settled that the claiming of a new function or unknown property which is inherently present in the prior art method will not make the claim patentable as set forth in the 102(b) rejection above.

(Office Action; p. 15). While applicants do not dispute that this line of reasoning could apply to composition(s) and Minin would arguably anticipate the invention if the instant claims were directed to a composition, but that is not the case here. The instant claims are directed to a newly discovered method of using these compounds to a specific patient population in need thereof. Contrary to the position taken by the Patent Office, it is well established in the patent law, that the discovery of a new use for an old composition based on unknown properties of the composition might be patentable to the discoverer as a process of use. This line of reasoning is also demonstrated in the second reference, *i.e.*, to Henry, cited by the Patent Office. Even though Minin was cited in the Henry reference, the Patent Office nonetheless issued a patent to Henry, contrary to the reasoning presented by the Patent Office herein. In other words, even if we say, for an argument sake, that Minin teaches a method of using luminol as an antioxidant, Minin does not anticipate the use of the cyclic bioisosteres to treat acidosis (or reversible abnormal changes of pH of cells of the living body) (claim 71), oxygen deficiency in cell (claim

86), increasing the aggregation of thrombocytes and erythrocytes (claim 97) or prophylaxis of decreasing the aggregation of thrombocytes and erythrocytes (instant claim 101) when administered to a subject in need of such treatment. These subjects would differ from the subjects that require antioxidants, which is contrary to the position taken by the Patent Office that "administering the same compound in the same amount to the same or similar patient population." (Office Action; p. 16).

Thus, applicants respectfully assert that Minin does not anticipate the claimed methods either expressly or inherently and respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. 102(b) as being anticipated by Minin.

Response to Rejections under 35 U.S.C. § 102(e)

Claims 71, 82, 85, 86, 90, 93-96, 99, 103, 104, 106, 108, and 110 have been rejected under 35 U.S.C. 102(e) as being anticipated by Henry, et al. (U.S. Patent 6,953,799, already of record). Specifically, the Patent Office holds that Henry discloses a compound such as luminol that can be allegedly administered to a patient to treat "hosts with diseases involving impaired or aberrant intracellular redox states, which affects the membrane proton gradient, resulting in intracellular acidosis, and causes oxygen deficiency in cells and excessive formation of the free radical superoxide" (Office Action; p. 18). The Patent Office points to column 2, lines 40-55 for support. Applicants thoroughly examined the cited reference and the above-identified section(s) and now must respectfully disagree with the position taken by the Patent Office.

The cited reference to Henry describes the use of the phthalazine diones to primarily support metabolically stressed cells in a host by buffering intracellular redox status. (Henry, col 2, lines 35-40 and col 4, lines 33-36). In particular, Henry suggests that the

compound should be administered to individuals or "hosts" upon "proper diagnosis of the thiol redox status of the aerobic metabolism in the stressed mitochondria," (emphasis added) preferably in combination with an oxidative protector. (Col. 4, line 65 – Col. 5, line 8). The redox reaction describe a process in which atoms have their oxidation number changed by loss or gain of electrons. In Example 1, Henry suggests that phthalazine dione is a thiol redox modulator that can quickly ameliorate the redox-induced edematous swelling. (Col. 5, lines 46-60). In Example 13, Henry describes the complexity of the mitochondrial permeability that is sensitive to thiol redox status because the specific mitochondrial channels are composed of two thiol redox-sensitive proteins. (Col. 12, lines 23-34). The Patent Office relies on this observation of proton gradient formation within mitochondria to suggest that Henry teaches treating acidosis. Applicants respectfully disagree.

First, in making this connection between the proton gradient formation within mitochondria and, for example, acidosis, the Patent Office relies on the principle of inherency (see MPEP 2112). However,

> "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.'" In re Robertson, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (cited in MPEP 2112; emphasis added)

Indeed, "[i]n relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (cited in MPEP 2112). Applicants

respectfully disagree that the proton gradient formation within mitochondria would necessary cause acidosis. "Intracellular pH is determined as a result of various biochemical processes concerned with energy metabolism and buffering capacity." (see Iwanaga et al. "Is the intracellular pH threshold and anaerobic threshold from the view point of intracellular events," *Appl Human Sci*, 15(2), 59-65, 59, 1996, a copy included). For example, pH regulation in the cells come from such mechanisms as (1) vacuolar H^+-ATPases, (2) Na^+/H^+ exchangers, (3) lactate$^-$-H^+ symporters, and (4) cation –dependent and independent anion exchangers. (see Fig. 1 of Shrode et al., "Role of Intracellular pH in Proliferation, Transformation and Apoptosis." *J Bioenergetics Biomem* 29(4), 1997, a copy included). Indeed, pH can change significantly under not only pathophysiological but also physiological circumstance and that changes in pH exert profound effects on the physiological and biophysical properties of cells. (see Takahashi et al. "Modulation of neuronal function in intracellular pH," *Neuroscience Research* 24, 109-116, 109, 1996, a copy included). Thus, contrary to the position taken by the Patent Office, the proton gradient formation within mitochondria does not necessarily translate to the reversible abnormal changes in pH because a redundancy of regulatory mechanisms for pH regulation that occur in the cell in concert, would balance pH to the physiologically acceptable levels for the overall cell function. (see Shrode et al. pg. 394, col 1, 2nd paragraph). In order words, the mere happenstance of the proton gradient formation within stressed mitochondria does not mean that the pH is changed to an abnormal level. "The mere fact that a certain thing may result from a given set of circumstances is not sufficient" to establish inherency. (see MPEP 2112).

Second, the proton gradient regulation in mitochondria is not caused by phthalazine dione, but comes about as the regulation of thiol redox-sensitive proteins responsible for the membrane permeability within either the inner matrix or intermembrane space of

mitochondria and not within the intracellular matrix of the cell. This is contrary to the method of treatment proposed in the instant application. Applicants have found that the claimed compound is capable of penetrating into the endocellular space and irreversibly attract up to 4 electrons and protons, thereby promoting an appreciable decrease of a metabolic endocellular acidosis, (¶. [0091] of the specification as published), which suggests a linear dependence of acidosis alleviation on the concentration of the compound. Indeed, applicants showed that the action of the claimed compound in pH regulation is similar to the action of the growth factors of serum or monensine ionophore between concentration of 0.2 to 20 mkg/ml. Id. at ¶. [0143]. Hence, those skilled in the art would not look to Henry in order to treat patients with, for example, acidosis or oxygen deficiency because being a regulator of thiol or oxygen redox potential differs from regulating an endocellular pH imbalance. Moreover, whereas Henry suggests that the compound should be administered to individuals or "hosts" upon "proper diagnosis of the thiol redox status of the aerobic metabolism in the stressed mitochondria," in the instant method, the compound should be administered to individuals that show a deviation in, for example, an endocellular pH from the physiologically acceptable levels that can be readily measured by among others a standard pH meter of the physiological fluid, *e.g.*, blood.

Third, lets say for an argument sake, in reading Henry those skilled in the art would understand that certain concentrations of phthalazine dione may actually cause the acidosis if a skilled artisan provides a high dose where a low dose should be given in order to stabilize the thiol redox status of the host's aerobic metabolism in the stressed mitochondria and vice versa. For example, a low dose may increase a proton gradient, whereas a high dose would stop the flow completely and potentially decrease the proton gradient. (see Col. 3, lines 5-20), although since Henry's invention is directed to use the compound as a thiol or oxygen redox

modulator, the effect on the pH or oxygen deficiency is not clear and merely speculative as noted above.

Thus, applicants respectfully assert that Henry does not anticipate the claimed methods either expressly or inherently because the mechanism of action of treatment has a direct bearing on which patient population is selected. While Henry teaches a method of regulating thiol or oxygen redox states, the patients would be selected that show redox imbalance of the aerobic metabolism in the mitochondria (col 4, line 65 – col. 5, line 2), whereas the instant method is directed to, among others, treating reversible abnormal changes in pH of nucleated and non-nucleated cells[1], by administering to a subject in need of such treatment a pharmaceutically-effective amount of a biologically-active compound in order to normalize the endocellular pH to the physiologically acceptable levels. The patients that have a pH imbalance may not necessarily be the same patients that have redox imbalance in the mitochondria and vice versa. Thus, those skilled in the art would not be able to impart from Henry that the compound in question may be used to treat pH imbalance. Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. 102(e) as being anticipated by Henry.

CONCLUSION

For at least the reasons stated above, Applicants respectfully request entry of this response and allowance of the claims. However, in the event that a telephone conference would facilitate examination of this application in any way, the Examiner is invited to contact the undersigned at the number provided. Favorable action by the Examiner is earnestly solicited.

[1] For example red blood cells are non-nucleated cells that do not have mitochondria.

DEPOSIT ACCOUNT AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees which may be required for consideration of this Amendment to Deposit Account No. 50-4827, Order No. 1004398-001US (4874-7000).

In the event that an extension of time is required, or which may be required in addition to that requested in a petition for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No 50-4827, Order No. 1004398-001US (4874-7000).

Respectfully submitted,

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